REFERENCE 1

```
ΑN
     132:175851 CA
     Pipecolic acid derivatives for vision and memory disorders
ΤI
     Ross, Douglas T.; Sauer, Hansjorg; Hamilton, Gregory S.; Steiner, Joseph
TN
     Guilford Pharmaceuticals Inc., USA
PΑ
SO
     PCT Int. Appl., 126 pp.
     CODEN: PIXXD2
DT
     Patent
     English
LA
     ICM A61K031-00
IC
     1-11 (Pharmacology)
CC
     Section cross-reference(s): 27
FAN.CNT 1
                                                APPLICATION NO.
                        KIND DATE
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               IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD,
              MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,
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          RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     AU 9955557
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                                              AU 1999-55557
                                                                  19990812
                         A1
PRAI US 1998-134417
                         19980814
     WO 1999-US18242 19990812
GΙ
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AB Pipecolic acid derivs. are prepd. for treating vision disorders, improving

Ι

vision, treating memory impairment, or enhancing memory performance in an animal. These compds. bind to immunophilin FKBP12 and preferably do not have immunosuppressive activity. Affinity for FKBP12 is measured as inhibition of prolyl peptidyl cis-trans isomerase (rotamase). Thus, pipecolic acid ester I inhibited rotamase with a Ki of 20 nM, showed a clearance rate of 41.8 .mu.L/min, and rescued 56.6% of optic nerve axons from degeneration 14 days after optic nerve transection in rats (dose and route of administration not stated).

ST pipecolate deriv prepn vision memory disorder; immunophilin FKBP12 ligand vision memory disorder

IT Proteins, specific or class

RL: BPR (Biological process); BIOL (Biological study); PROC (Process) (FKBP (FK 506-binding protein); pipecolic acid derivs. for vision and memory disorders)

IT Proteins, specific or class

RL: BPR (Biological process); BIOL (Biological study); PROC (Process) (FKBP-12 (FK 506-binding protein, 12,000-mol.-wt.); pipecolic acid

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derivs. for vision and memory disorders)
ΙT
     Eye
        (conjunctiva, disorder; pipecolic acid derivs. for vision and memory
        disorders)
ΙT
        (cornea, disorder; pipecolic acid derivs. for vision and memory
        disorders)
ΙT
     Immunity
        (disorder, of eye; pipecolic acid derivs. for vision and memory
        disorders)
ΙT
     Lacrimal gland
     Memory, biological
        (disorder; pipecolic acid derivs. for vision and memory disorders)
TT
     Memory, biological
        (enhancement of; pipecolic acid derivs. for vision and memory
        disorders)
ΙT
     Radicals, biological studies
     RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
        (eye disorders mediated by; pipecolic acid derivs. for vision and
        memory disorders)
ΙT
        (improvement of; pipecolic acid derivs. for vision and memory
        disorders)
IT
     Eye, disease
        (injury; pipecolic acid derivs. for vision and memory disorders)
IT
        (lid, disorder; pipecolic acid derivs. for vision and memory
disorders)
     Aging, animal
IT
        (memory impairment in; pipecolic acid derivs. for vision and memory
        disorders)
IT
     Structure-activity relationship
        (neuroprotectant; pipecolic acid derivs. for vision and memory
        disorders)
IT
     Cytoprotective agents
        (neuroprotectants; pipecolic acid derivs. for vision and memory
        disorders)
ΙT
     Brain
        (optic tract, disorder; pipecolic acid derivs. for vision and memory
        disorders)
ΙT
     Nerve
        (optic, disorder; pipecolic acid derivs. for vision and memory
        disorders)
    Cataract
IΤ
     Eye, disease
     Oligodendrocyte
        (pipecolic acid derivs. for vision and memory disorders)
TТ
     Immunophilins
     RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
        (pipecolic acid derivs. for vision and memory disorders)
     Eye, disease
ΙT
        (retinopathy; pipecolic acid derivs. for vision and memory disorders)
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        (uvea, disorder; pipecolic acid derivs. for vision and memory
        disorders)
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     95076-93-0, Rotamase
     RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
        (inhibition of; pipecolic acid derivs. for vision and memory
disorders)
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     preparation); THU (Therapeutic use); BIOL (Biological study); PREP
     (Preparation); USES (Uses)
        (pipecolic acid derivs. for vision and memory disorders)
     535-75-1D, Pipecolic acid, derivs. 53123-88-9, Rapamycin 141084-63-1
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       (pipecolic acid derivs. for vision and memory disorders)
    122-97-4, 3-Phenyl-1-propanol 2133-40-6, L-Proline methyl ester
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                   5781-53-3, Methyl oxalyl chloride 28276-08-6,
    hydrochloride
    1,1-Dimethylpropylmagnesium chloride
    RL: RCT (Reactant)
       (pipecolic acid derivs. for vision and memory disorders)
                  186268-77-9P 186268-78-0P
ΙT
    139419-63-9P
    RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
       (pipecolic acid derivs. for vision and memory disorders)
REFERENCE 2
ΑN
    132:26633 CA
    Pipecolic acid derivatives for hair growth compositions
ΤI
ΙN
    Hamilton, Gregory S.; Steiner, Joseph P.
    Guilford Pharmaceuticals, Inc., USA
PΑ
SO
    PCT Int. Appl., 103 pp.
    CODEN: PIXXD2
DT
    Patent
LA
    English
    ICM A61K007-48
IC
    ICS A61K031-50; A61K031-435; A61K031-445; C07K005-02; C07K005-08
CC
    62-3 (Essential Oils and Cosmetics)
    Section cross-reference(s): 63
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    WO 9962483 A1 19991209 WO 1998-US11242 19980603
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PRAI WO 1998-US11242 19980603
    This invention relates to pharmaceutical compns. and methods for treating
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145021-41-6

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alopecia and promoting hair growth using pipecolic acid derivs.
    hair lotion contained 95% EtOH, a pipecolic acid deriv. such as
     4-(4-methoxyphenyl) butyl 1-(2-oxo-2-phenylacetyl)-2-piperidinecarboxylate
     10.0, .alpha.-tocopherol acetate 0.01, ethoxylateed hardened castor oil
     0.5, and water 9.0%, and perfume and dye.
    pipecolic acid deriv hair growth
ST
ΙT
    Hair preparations
        (creams; pipecolic acid derivs. for hair growth compns.)
ΙT
     Hair preparations
        (emulsions; pipecolic acid derivs. for hair growth compns.)
IT
     Hair preparations
        (growth stimulants; pipecolic acid derivs. for hair growth compns.)
     Hair preparations
ΙT
        (lotions; pipecolic acid derivs. for hair growth compns.)
ΙT
     Alopecia
     Immunosuppressants
     Shampoos
        (pipecolic acid derivs. for hair growth compns.)
IT
     Immunophilins
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (pipecolic acid derivs. for hair growth compns.)
     535-75-1D, Pipecolic acid, derivs.
                                          53123-88-9, Rapamycin
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     RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL
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        (pipecolic acid derivs. for hair growth compns.)
RE.CNT
(1) Armistead, D; US 5620971 A 1997 CAPLUS
(2) Astra Aktiebolaget; WO 9611943 A 1996 CAPLUS
(3) Fujisawa Pharm Co Ltd; EP 0423714 A 1987 CAPLUS
(4) Guilford Pharm; WO 9813343 A 1998 CAPLUS
(5) Nelson, F; US 5385908 A 1995 CAPLUS
(6) Skotnicki, J; US 5252579 A 1993 CAPLUS
REFERENCE 3
     128:70783 CA
AN
     Pipecolic acid derivative inhibitors of rotamase enzyme activity
TΙ
effective
     at stimulating neuronal growth
IN
     Steiner, Joseph P.; Snyder, Solomon; Hamilton, Gregory S.
     GPI NIL Holdings, Inc., USA; Johns Hopkins Univ. School of Medicines
PA
     U.S., 47 pp. Cont.-in-part of U.S. Ser. No. 474,072.
SO
     CODEN: USXXAM
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     ICM A61K031-445
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NCL 514317000
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     A method is disclosed for using neurotrophic pipecolic acid deriv.
     having an affinity for FKBP-type immunophilins as inhibitors of the
enzyme
     activity assocd. with immunophilin proteins, and particularly inhibitors
     of peptidyl-prolyl isomerase or rotamase enzyme activity to stimulate or
     promote neuronal growth or regeneration. The compds. of the invention
are
     useful for treatment of neurol. disorders.
     neuron growth pipecolate deriv rotamase inhibitor; regeneration neuron
ST
     pipecolate deriv rotamase inhibitor; neurol disorder pipecolate deriv
     rotamase inhibitor
ΙT
     mRNA
     RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
        (FKBP and GAP-43; pipecolic acid deriv. inhibitors of rotamase enzyme
        activity for stimulating neuronal growth and regeneration and treating
        neurol. disorders)
     Transport (biological)
ΙT
        (FKBP; pipecolic acid deriv. inhibitors of rotamase enzyme activity
for
        stimulating neuronal growth and regeneration and treating neurol.
        disorders)
IT
     Stroke
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(brain damage-assocd.; pipecolic acid deriv. inhibitors of rotamase enzyme activity for stimulating neuronal growth and regeneration and

```
treating neurol. disorders)
IT
    Nerves
        (facial; pipecolic acid deriv. inhibitors of rotamase enzyme activity
        for stimulating neuronal growth and regeneration and treating neurol.
        disorders)
ΙΤ
     Growth factors (animal)
     RL: BAC (Biological activity or effector, except adverse); BIOL
     (Biological study)
        (neurite extension factors; pipecolic acid deriv. inhibitors of
        rotamase enzyme activity for stimulating neuronal growth and
        regeneration and treating neurol. disorders)
     Alzheimer's disease
     Amyotrophic lateral sclerosis
     Brain injury
     Nerve degeneration
     Nervous system agents
     Nervous system diseases
     Neurons
     PC12 cell
     Parkinson's disease
     Peripheral nerve injury
     Peripheral neuropathy
     Sciatic nerve
     Spinal cord injury
     Spinal ganglion
        (pipecolic acid deriv. inhibitors of rotamase enzyme activity for
        stimulating neuronal growth and regeneration and treating neurol.
       disorders)
ΙT
     FKBP (protein)
     FKBP12 (protein)
     GAP-43 (protein)
     Immunophilins
    Myelin
     RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
        (pipecolic acid deriv. inhibitors of rotamase enzyme activity for
        stimulating neuronal growth and regeneration and treating neurol.
        disorders)
     Brain-derived neurotrophic factor
ΙT
    Ciliary neurotrophic factor
    Glial-derived neurotrophic factor
     Neurotrophic factors
     RL: BAC (Biological activity or effector, except adverse); THU
     (Therapeutic use); BIOL (Biological study); USES (Uses)
        (pipecolic acid deriv. inhibitors of rotamase enzyme activity for
        stimulating neuronal growth and regeneration and treating neurol.
        disorders, and use with neurotrophic factors)
                                                              59865-13-3,
IT
     9061-61-4, Nerve growth factor
                                      53123-88-9, Rapamycin
     Cyclosporin A
                    149438-31-3, WAY-124466
     RL: BAC (Biological activity or effector, except adverse); BIOL
     (Biological study)
        (pipecolic acid deriv. inhibitors of rotamase enzyme activity for
        stimulating neuronal growth and regeneration and treating neurol.
        disorders)
ΙT
     104987-11-3
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(Biological
     process); BIOL (Biological study); PROC (Process)
        (pipecolic acid deriv. inhibitors of rotamase enzyme activity for
        stimulating neuronal growth and regeneration and treating neurol.
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186834-82-2 186834-83-3

186834-87-7 186834-88-8 200417-73-8 200728-03-6 200728-04-7 RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (pipecolic acid deriv. inhibitors of rotamase enzyme activity for stimulating neuronal growth and regeneration and treating neurol. disorders)

IT 9025-75-6, Calcineurin 95076-93-0, Rotamase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
 (pipecolic acid deriv. inhibitors of rotamase enzyme activity for stimulating neuronal growth and regeneration and treating neurol. disorders)

ΙT

130939-66-1, Neurotrophin 3
RL: BAC (Biological activity or effector, except adverse); THU
(Therapeutic use); BIOL (Biological study); USES (Uses)
(pipecolic acid deriv. inhibitors of rotamase enzyme activity for stimulating neuronal growth and regeneration and treating neurol.

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L27 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
     53123-88-9 REGISTRY
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CN
     Rapamycin (9CI)
                      (CA INDEX NAME)
OTHER CA INDEX NAMES:
     23,27-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine, rapamycin
     deriv.
OTHER NAMES:
     (-)-Rapamycin
CN
CN
     (3S, 6R, 7E, 9R, 10R, 12R, 14S, 15E, 17E, 19E, 21S, 23S, 26R, 27R, 34aS) -
     9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-
     dihydroxy-3-[(1R)-2-[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-
     methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-
     pyrido[2,1-c][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-
     pentone
CN
     23,27-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine-
     1,5,11,28,29(4H,6H,31H)-pentone,
9, 10, 12, 13, 14, 21, 22, 23, 24, 25, 26, 27, 32, 33,
34,34a-hexadecahydro-9,27-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-
     methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-,
[3S-[3R*[S*(1R*,3S*,4S*)],6S*,7E,9S*,10S*,12S*,14R*,15E,17E,19E,21R*,23R*,
     26S*,27S*,34aR*11-
CN
     Antibiotic AY 22989
CN
     AY 22989
CN
     Rapamune
     SIIA 9268A
CN
CN
     Sirolimus
[3S-[3R*[S*(1R*,3S*,4S*)],6S*,7E,9S*,10S*,12S*,14R*,15E,17E,19E,21R*,23R*,
     26S*, 27S*, 34aR*]]-9, 10, 12, 13, 14, 21, 22, 23, 24, 25, 26, 27, 32, 33, 34, 34a-
     Hexadecahydro-9,27-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-
     methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-
     pyrido[2,1-c][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-
     pentone
FS
     STEREOSEARCH
     C51 H79 N O13
MF
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LC
                  ADISINSIGHT, AGRICOLA, AIDSLINE, ANABSTR, BEILSTEIN*,
       BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CEN,
       CHEMCATS, CHEMINFORMRX, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT,
       DRUGU, DRUGUPDATES, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE,
MRCK*,
       MSDS-OHS, NAPRALERT, PHAR, PROMT, RTECS*, SYNTHLINE, TOXLINE, TOXLIT,
       USAN, USPATFULL, VETU
         (*File contains numerically searchable property data)
     Other Sources:
                      WHO
Absolute stereochemistry.
Double bond geometry as shown.
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PAGE 2-A
Me

1328 REFERENCES IN FILE CA (1967 TO DATE)
77 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1334 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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L19 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2001 ACS
     . . . isomerase or rotamase enzyme activity, to stimulate or promote
ΑB
     neuronal growth or regeneration. The compds, of the invention (e.g.
     Way-124,666; SLB-506) are useful for the treatment of
     neurol. disorders. The compds. may be used in conjunction with a neurotrophic factor (neurotrophic. . .
                           1997:151523 CAPLUS
ACCESSION NUMBER:
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DOCUMENT NUMBER: 126:152817

Pipecolic acid derivatives as inhibitors of rotamase TITLE:

activity, and use in treatment of nervous system

disorders.

Steiner, Joseph P.; Snyder, Solomon; Hamilton, INVENTOR(S):

Gregory

S.

Guilford Pharmaceuticals Inc., USA; Johns Hopkins PATENT ASSIGNEE(S):

University School of Medicine

SOÛRCE: PCT Int. Appl., 110 pp.

CODEN: PIXXD2

DOCUMENT TYPE: LANGUAGE:

Patent English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

							APPLICATION NO.				DATE						
				A1 19961219			WO 1996-US9561										
	W:													CZ,			
														KΖ,			
		•	•	LV,	MD,	MG,	MK,	MN,	MW,	MX,	NO,	NΖ,	PL,	PT,	RO,	Rυ,	SD,
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	RW:													FI, CM,			GK,
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	R: 9608 9604 9604 9601 9704	BE,	FR,	GR,	ΙE,	ΙΤ,	MC,	NL				•					
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L25 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS

RN 149438-31-3 REGISTRY

CN 27,31-Epoxy-5,36-etheno-1H,5H-pyrido[2,1-c][1,2,4]triazolo[1,2-

q][1,4,17,18]oxatriazacyclohentriacontine-1,3,9,15,19,25,26(2H,6H,10H,19aH)-heptone,7,8,11,14,16,17,20,21,22,23,27,28,29,30,31,32,33,36-octadecahydro-11,27-dihydroxy-17-[(1R)-2-[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,33-dimethoxy-6,8,12,14,28,34-hexamethyl-2-phenyl-,

(6S, 8R, 10R, 11R, 12E, 14R, 17S, 19aS, 27R, 28R, 31S, 33S, 34E) -

(9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 27,31-Epoxy-5,36-etheno-1H,5H-pyrido[2,1-c][1,2,4]triazolo[1,2-

q][1,4,17,18]oxatriazacyclohentriacontine-1,3,9,15,19,25,26(2H,6H,10H,19aH)-heptone, 7,8,11,14,16,17,20,21,22,23,27,28,29,30,31,32,33,36-octadecahydro-11,27-dihydroxy-17-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethyl]-10,33-dimethoxy-6,8,12,14,28,34-hexamethyl-2-phenyl-,

[6S-[6R*,8S*,10S*,11S*,12E,14S*,17R*[S*(1R*,3S*,4S*)],19aR*,27S*,28S*,31R*,33R*,34E]]-[partial]-

OTHER NAMES:

CN WAY 124466

FS STEREOSEARCH

MF C59 H84 N4 O15

SR CA

LC STN Files: CA, CANCERLIT, CAPLUS, MEDLINE, TOXLINE, TOXLIT, USPATFULL

Ring System Data

Elemental Analysis EA	Elemental Sequence ES +=========	the Rings SZ	Ring System Formula RF	Identifier RID	Count
C6 C6 C2N3-C4N2- C5N-C5O-	C6 C6	6 6 5-6-6-6-29 	C6 C6	 46.150.1 46.150.18 55790.1.1 	1 1

Absolute stereochemistry. Double bond geometry as described by E or Z. Currently available stereo shown.

10 REFERENCES IN FILE CA (1967 TO DATE)